

B. State of the Claims

Claims 38-40, 52-61, 63-68, 70-75 and 100-103 are currently pending. Claim 38 has been amended to more particularly claim the invention. Support for the amendment may be found throughout the examples and the specification. See, for example, page 124 of the specification describing cells expressing TLR-4 as a result of transformation. The balance of the specification provides for cells naturally expressing or altered or induced to express TLR-4.

A marked version of the amendments to the claims is provided in Appendix A. A clean version of the pending claims as amended is provided for the Examiner's convenience in Appendix B.

C. The Claims are Definite Under 35 U.S.C. § 112, Second Paragraph

Claims 38-40, 52-61, 63-68, 70-75, and 100 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Applicants respectfully traverse this rejection.

i) The name TLR-4 is an art accepted term and definite in its meaning in light of the specification.

The Action maintains the rejection of claims 38, 40, 52, 55, 56, and 63-64 on the grounds that "the art nor specification disclose the structural and functional properties which must be present for the polypeptide to be classified as a TLR-4 polypeptide." The Action at page 2, lines 12-13 and page 4, lines 7-8. The Action also concludes that since name of TLR-4 has changed once in the literature such changes render the use of the term TLR-4 indefinite. The Action at pages 2-3 and page 4, paragraph 3. The Action further notes that proteins of a different name may exist that share the same structure and properties as that named as TLR-4. Applicants respectfully traverse.

A proper evaluation of the claims under the second paragraph of 35 U.S.C. § 112 requires that the claims be read in light of the specification as interpreted by one of ordinary skill in the art. *North Am. Vaccine, Inc. v. American Cyanamid Co.*, 7 F.3d 1571, 1579, 28 USPQ2d 1333, 1339 (Fed. Cir. 1993); *In re Moore*, 439 F.2d 1232, 1235 (C.C.P.A. 1971). Furthermore, the law does not require that only immutable or invariant terms be used in claim language. Inventors are encouraged to use concise language, as long as it is reasonably definite in view of the specification. This is long established law. *North Am. Vaccine, Inc.*, 7 F.3d 1571 at 1579; *Miles Lab., Inc. v. Shandon, Inc.*, 997 F.2d 870, 875, 27 USPQ2d 1123, 1126 (Fed. Cir. 1993); *Loom Co. v. Higgins*, 105 U.S. (Otto.) 580, 586 (1881).

Applicants have provided a detailed and consistent definition of TLR-4 in the specification. Most particularly, TLR-4 as used by the Applicants in describing particular embodiments refers explicitly to polypeptides of the sequences of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99 and those sequences at least about 85% similar thereto or biologically functional equivalents thereof. See the specification at page 30, lines 4-15 and page 73, line 18 through page 76, line 11, and Example 8, pages 105-122. In view of the properties and structures of TLR-4 polypeptides thus supplied in the present specification Applicants respectfully submit that the specification sheds sufficient light upon the claims to render them clear and definite to one of skill in the art under the second paragraph of 35 U.S.C. § 112.

Applicants also respectfully point out that the law does not require that the Applicants define in the specification every term of art well known to the artisan. Use of a well known term of art in the specification without detailed definitions thereof does not render claims utilizing that same language indefinite. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1556-58,

220 USPQ 303, 315-16 (Fed. Cir. 1983). Claims may therefore make use of the language understood by those of skill in the art without additional, detailed definitions in the written description. *Id.* Where later developed terms are arguably more definite than the terms available near the filing date, later accepted and more precise terms are favored. *In re Fisher*, 427 F.2d 833, 838 (C.C.P.A. 1970). The name TLR-4 is in common use among artisans in the field in exactly the sense in which the Applicants have defined it. Although the referenced polypeptide may have once been named Toll-4, use of the more current and more current and precise term TLR-4 (or TLR4) cannot render the claims indefinite. *In re Fisher* at 838.

Indeed, the identity of TLR-4 within the family of Toll-like receptors is unambiguous, as is known to those of skill in the art. Applicants provide as Appendix C articles by Du *et al.*, and Rock *et al.*, which are examples of the scientific literature indicative of the knowledge available to one of skill in the art to define and recognize TLR-4 polypeptides. Du *et al.* provide sequence data for each of ten TLRs (Toll-like receptors), alignments of their sequences (Figure 2, of Du *et al.*), and analysis of the evolutionary divergence of TLR-4 from the lineages bearing the remaining members of the family. The uniquely shared derived sequence characteristics of the TLR-4 clade, exemplified in Figures 4 and 5 of Du *et al.* are clear signposts to TLR-4 identity available to the ordinary artisan. Similarly, Rock *et al.* provides unique sequence characteristics found in each functional domain of each member of the Toll-like receptor family. See Figures 2 and 3 of Rock *et al.*

Applicants respectfully submit, that in view of the above, one of ordinary skill in the art would find the language of the claims definite in light of the specification. Applicants therefore respectfully submit that claims 38-40, 52-68, 70-75 are not indefinite under the second paragraph of 35 U.S.C. § 112 and request that the rejection be withdrawn.

ii) Lipopolysaccharide mediated responses are clear and well known to those of skill in the art.

Claims 52 and 101-103 are rejected on the grounds that they are indefinite because the phrase “mediation of the lipopolysaccharide mediated response” is allegedly not clear. Claims 38, 40 and 52 are rejected because the phrase “liposaccharide mediated response” is allegedly unclear. The Action queries “where does the lipopolysaccharide pathway begin and end?” The Action, page 3, lines 11-12. Applicants respectfully traverse.

In response to the previous argument in rejection, Applicants have referred to the specification at page 2, line 14 through page 4, line 24, and especially page 22 lines 3-7 for a succinct description of the events and circumstances that comprise the initiation of a response to LPS and the resultant responses. Further, exemplary parameters and methods for measuring and determining the response are found in several locations in the specification: page 87, line 5 through page 88, line 15, Example 2 (page 95, line 25 through page 96, line 18), and Example 9 (page 123, line 1 through page 129, line 20).

In the section of the Specification titled “Assays for LPS responsiveness” two examples of LPS-mediated response assays are described: a splenocyte proliferation assay and a macrophage response assay. See the specification at page 87, line 8 to page 88, line 15. The splenocyte response assay compares the proliferation of splenocytes incorporating tritiated thymidine (as measured by counts per minute, CPM) with and without stimulation with LPS. The macrophage response assay measures the per cent of cytotoxicity due to TNF released by cells in response to LPS. In yet another means of assaying for LPS response, TNF production may be directly measured. See the specification at page 3, lines 7-13, FIG. 15C, and page 87, line 23 through page 88, line 7.

These are exemplary parameters and methods for measuring the LPS response. The specification thereby provides concrete examples, methods, and standards for measuring responses to LPS endotoxin mediated through TLR-4. Applicants respectfully call attention to these passages.

Additional methods and parameters are available to the ordinary artisan through the knowledge of one of skill in the art. Applicants respectfully reiterate that the law does not require that the Applicants define in the specification every term of art well known to the artisan. Use of a well known term of art in the specification without detailed definitions thereof does not render claims utilizing that same language indefinite. *W.L. Gore & Assoc., Inc.* 721 F.2d 1540, 1556-58. If necessary, a standard reference work may inform the reading of the specification, and if so, that in itself does not render claims utilizing that language indefinite. *Atmel Corp. v. Information Storage Devices, Inc.*, 198 F.3d 1374, 1382 (Fed. Cir. 1999) (“...even a dictionary or other documentary source may be resorted to...”).

Applicants have supplied as Appendix D passages from the reference work “Medical Microbiology, 4th Ed.” S. Baron, ed., 1996, University of Texas Medical Branch at Galveston, Galveston, TX., pages 130-133, as an example of a standard reference work that verifies that a lipopolysaccharide mediated response is well understood by those of skill in the art. The passages are a mere summary of the extensive literature in the field of endotoxin biology as it existed in 1996, but nevertheless serves to demonstrate that one of skill in the art would know the metes and bounds of a LPS mediated response. As indicated in the Applicants’ specification at page 2, line 20, and as is well known and readily apparent to one of skill in the art, lipopolysaccharide is a term synonymous with endotoxin (see Medical Microbiology at page 130, column 2, 4th paragraph, under the heading “Structure of Endotoxin”).

Further, and as is well known and readily apparent to one of skill in the art, “The biologic effects of endotoxin [LPS] have been extensively studied” Medical Microbiology at page 131, column 1, under heading “Biologic Activity of Endotoxin.” Thus, LPS mediated responses at least include (as of 1996) those activities listed in Table 7-4, page 132 of Medical Microbiology. Indeed, the central importance of LPS in the mediation of cellular responses to a variety of conditions is clear and well known to the ordinary artisan.

At the time of this summary (1996), the specific mechanism of cellular response was not clear. See Medical Microbiology at page 132, bottom of column 1, extending to the top of column 2. What was clear was that the host cell exposure to endotoxin was key to the “myriad sequelae” that exposure to endotoxin produces. “It does seem clear that the host cellular response to endotoxin, rather than a direct toxic effect of endotoxin, plays the major role in causing tissue damage.” Medical Microbiology, page 132, top of column 2. Indeed, it is the Applicants’ discovery that TLR-4 polypeptide plays the key role as a cell’s LPS receptor and is, therefore the key in the pathway leading to the various responses to certain types of infection. “[T]he demonstration that *Lps* is identical to TLR-4 leaves no room for doubt that TLR-4 is essential for LPS signalling.” The specification at page 104, lines 14-15. This discovery therefore identifies *the* pathway, *i.e.* through TLR-4, by which these responses are mounted.

As an example of the broad acceptance of Applicants’ discoveries by those of skill in the art, and the importance and clarity of TLR-4’s role in LPS signalling, Applicants provide as Appendix E a recent paper in the journal Nature, which discusses and builds upon Applicants’ discoveries.

The clarity that Applicants’ discovery provides is engendered in the terms of the claims. Thus, the methods require “obtaining a cell expressing a TLR-4 polypeptide” and “measuring a

lipopolysaccharide mediated response mediated by the TLR-4 polypeptide.” See claim 38. The Applicants’ specification provides explicit means by which one may measure a LPS response mediated by the TLR-4 polypeptide and the skill of the art provides even more.

Applicants respectfully submit that the claims are definite under the second paragraph of 35 U.S.C. § 112 when properly viewed in light of the ordinary skill of one in the relevant art and the detailed descriptions available to the artisan in the applicants specification. Applicants therefore respectfully request that the rejections be withdrawn.

iii) The terms “small molecule inhibitor” are well known in the art and their meaning is not indefinite.

The meaning of the terms “small molecule inhibitor” is well established as referring to small molecules that inhibit whatever activity is involved in their application.

iv) The meaning of the terms “a stimulator of immune response” is provided in the specification and is also well known in the art and is therefore not indefinite.

The Action rejects claim 71 under the second paragraph of 5 U.S.C. § 112 because the terms “stimulator of an immune response” are said to be lacking in structural limitations of the modulator and stimulated immune response. Applicants respectfully traverse.

Applicants again respectfully note that evaluation of the claims under the second paragraph of 35 U.S.C. § 112 requires that the claims be read in light of the specification and that Applicants need not define in the specification every term of art well known to the relevant artisan. *North Am. Vaccine, Inc.*, 7 F.3d 1571 at 1579; *W.L. Gore & Assoc., Inc.*, 721 F.2d 1540, 1556-58. Additionally, “under current law the specification of a patent consists of, and contains, both a written description of the invention and the claims.” *In re Dossel*, 115 F.3d 942, 945 (Fed. Cir. 1997).

Stimulation of immune responses is a well known effect of the administration of compounds such as interferon and cytokines. Further, the structural definitions of cytokines and interferons and their stimulatory effects on the immune system are well known in the art. Indeed, the meaning of claim 71 is made clear at least in part by reference to claims 72 and 73, which depend from claim 71. Claim 72 recites the limitation “wherein said stimulator of an immune response is a cytokine.” Claim 73 recites “wherein said stimulator of an immune response is an interferon.” The structural limitations of a stimulator of an immune response are therefore typified by cytokines and interferons.

Applicants respectfully submit that claim 71, viewed in light of the specification, which includes the claims, is not indefinite under the second paragraph of 35 U.S.C. § 112.

v) Summary

Applicants respectfully submit that claims 38, 40, 52, 55, 56, 62-64 and the claims depending upon them are not indefinite under 35 U.S.C. § 112, second paragraph. Applicants respectfully request withdrawal of the rejections.

D. The Pending Claims are Enabled.

The Action rejects claims 38-40, 52-61, 63-68, 70-75 and 100-103 under the first paragraph of 35 U.S.C. § 112. The Action alleges that the only screening method enabled is that which results in the altered expression of TLR-4 of SEQ ID NOS: 2, 4, 6, 98, or 99. Therefore, the Action concludes, methods of screening for modulators of LPS mediated responses through their interaction with TLR-4 are not enabled. Applicants respectfully traverse.

The pending claims are directed to methods of screening for modulators of a lipopolysaccharide mediated response that compare the response before and after contact of

TLR-4 with a putative modulator or candidate substance. Altered expression of TLR-4 of SEQ ID NOS: 2, 4, 6, 98, or 99 may be *one* mode of LPS response that is measured, but it is not the sole means of measuring TLR-4 mediated LPS responses disclosed by the specification.

In Applicants' previous response filed November 14, 2001, Applicants respectfully suggested that the Action mistakenly construed the nature of TLR-4 action and the character and scope of the invention. To clarify further, TLR-4 is the key component of the signaling pathway that results in, for example, an increase TNF production as a result of lipopolysaccharide contact with cell surface receptors. Signaling in such a pathway is clearly described as involving multiple physical contacts among pathway components and other cellular constituents. See, for example, the specification at page 123, line 1 through page 129, line 20. Moreover, the role of TLR-4 in the signalling pathway is now widely accepted by the field. As an example of the broad acceptance of Applicants' discoveries, Applicants provide as Appendix E a recent paper in the journal Nature, which discusses and builds upon Applicants' discoveries.

The sensitivity of the LPS mediated response may be directly effected by the endogenous levels of TLR-4 expression, but the LPS response itself may also be modulated by the nature of the physical interactions of TLR-4 with the other components of the pathway. Thus, altered isoforms of TLR-4, when co-expressed, interact with TLR-4 in modulating LPS mediated response. Another example of such effects includes the modulation of the intensity of the TLR-4 mediated response through interactions with interferon. See the specification at page 128, lines 20-26. Hence, modulation of LPS response through the modulation of TLR-4 activity, not merely its expression, is described and enabled by the specification as understood by those of skill in the art.

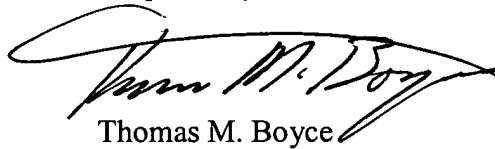
In view of the disclosure provided in the specification and the clarification provided above, Applicants respectfully submit that the claims are enabled and that the rejection be withdrawn.

E. Conclusion

Applicants have submitted remarks which are believed to place the present claims in condition for allowance. In view of this, Applicants respectfully request that the present claims be passed for allowance. Should the Examiner have any comments or questions with regard to any statements contained herein, or any suggestions as to claim modification, the Examiner is respectfully requested to contact the Applicants' representative listed below.

Please date-stamp and return the enclosed postcard evidencing receipt of these materials.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Thomas M. Boyce", written over a horizontal line.

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APPENDIX A

CLAIMS MARKED FOR AMENDMENT IN USSN 09/396,985.

Underline indicates insertion. ~~Strikethrough~~ indicates deletion.

38. (Three Times Amended) A method of screening for modulators of a lipopolysaccharide mediated response comprising the steps of:

- a) obtaining a cell expressing a TLR-4 polypeptide;
- b) measuring a lipopolysaccharide mediated response mediated by the TLR-4 polypeptide;
- c) contacting the TLR-4 polypeptide with a putative modulator;
- d) assaying for a change in the lipopolysaccharide mediated response; and
- e) comparing the lipopolysaccharide mediated responses mediated by the TLR-4 polypeptide obtained in steps b) and d) above

wherein a difference in the lipopolysaccharide mediated responses indicates that the putative modulator is a modulator of a lipopolysaccharide mediated response.